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The Role of Hyposthenuria in Enuresis among Paediatric Patients with Sickle Cell Disease

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Abstract

***Objectives*:** Enuresis in children with sickle cell disease (SCD) is common. Many risk factors have been postulated but its relation to hyposthenuria is debatable. This study aims to determine the prevalence of enuresis inchildren with SCD in Basrah, Iraq and to examine its relation with hyposthenuria. ***Methods*:** A cross-sectional epidemiological study was performed on children with SCD who met the inclusion criteria at the Basrah Center for Hereditary Blood Diseases over the period from the first of December 2020 through May 2021. A questionnaire was used to collect relevant data. Blood samples were tested for hemoglobin genotype, certain blood indices, and serum hemoglobin. Urine was tested for albumin and creatinine, and the specific gravity was measured using urine dipsticks. The relationships between enuresis and various sociodemographic and clinical variables were assessed. Binary logistic regression analysis was done to examine the independent risk factors of enuresis. ***Results*:** Out of 200 eligible children, 161 were studied after exclusion of 39 based on the exclusion criteria, yielding an 80.5% response rate, 60.9% of them were males. The mean age of the participants was 10.9 ± 2.9 years. Enuresis was reported in 50 (31.1%) patients. The independent risk factors for enuresis were; family history

of enuresis (OR, 5.94; 95% CI, 2.54-13.89; *P*<0.001), hyposthenuria (OR, 3.76, 95% CI, 1.25-11.30; *P*= 0.018), and sleep disorders (OR, 2.90; 95% CI, 0.19-7.06; *P*= 0.019). ***Conclusion*:** Enuresis is common among children with SCD. Hyposthenuria was significantly associated with enuresis. Family history of enuresis, and sleep disorders were also found to be significantly related to enuresis.
***Keywords*:** Enuresis, sickle cell disease, children, prevalence, hyposthenuria

Advances in Knowledge

- Enuresis is prevalent in sickle cell disease children (SCD). The role of hyposthenuria as a determinant of enuresis is controversial. This study revealed hyposthenuria as significant predictor of enuresis in children with SCD.

- To the best of the authors' knowledge, this study is the first in Iraq that attempts to examine the association between hyposthenuria and enuresis in SCD children.

Application to Patient Care

The results of this study may help understand the mechanisms underlying the enuresis in children with SCD.

Introduction

Sickle cell disease (SCD), an autosomal-recessive hemoglobin disorder, is one of the most common heritable diseases in the world.[1] Some Eastern Mediterranean countries, including Iraq, have also reported the disease. In Basrah, Iraq, 6.48% of the population has the sickle cell trait. [2] Enuresis is more common in children with SCD than in those with normal hemoglobin; however, prevalence rates vary widely, ranging from 26.4% to 51% depending on study methodology and enuresis definition criteria.[3]

SCD is a multisystem disease, with one of the most typically afflicted organs being the kidneys due to medullary ischemia and infarction. The underlying etio-pathogenesis of enuresis in SCD is not fully known. It has been related to tubular dysfunction manifested as defects in urinary concentration (hyposthenuria) and acidification, [4] low functional bladder capacity and high overnight urine volume, [3,5] glomerular hyperfiltration caused by increased prostaglandin production. [6] Eneh et al,

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on the other hand, revealed that enuresis in children with SCD is related to other causative variables that are common in the general population rather than hyposthenuria. [7] Similarly, other studies revealed that potential mechanisms underlying nocturnal enuresis in patients with normal hemoglobin genotype (hemoglobin AA) are equally relevant in SCD patients. [5,8]

The debatable role of hyposthenuria as a predictor of enuresis in SCD patients, as well as the lack of studies on the subject in Basrah, Iraq justified the conduct of this study, which aimed to verify the role of hyposthenuria in enuresis among SCD children.

Methods

Study setting, design, and patients

This was an analytical cross-sectional study including a non-probability convenient sample of 200 children with steady state SCD consecutively attending the Basrah Center for Hereditary Blood Diseases during the period from the first of December 2020 through May 2021. Subjects having diabetes mellitus, epilepsy, features of urinary tract infection, isolated daytime incontinence, known renal dysfunction/ impairment, diabetes insipidus, and on desmopressin or diuretic medication were excluded from the study. Of the 200 eligible children, 34 children were excluded because they either reported a history of recurrent urinary tract infection or were proven to have it by urine analysis. Other exclusion criteria led to the exclusion of five more children. The final studied sample size is made up of the remaining 161 children (80.5%).

Data collection & definition of variables

Patients and / or their parents were interviewed using a structured questionnaire that was developed for this study and completed by one of the researchers. It consisted of two parts; the first part contained information about the child's and parents' sociodemographic features (age, sex, and birth order of the child, exposure to stressful life event such as death or divorce of parents, number of siblings, parental level of education, and monthly family income). Parents were asked if any of the following life events had occurred in the family within the last 12 months; death or divorce of parent, death of someone in close proximity, child moving to another address or school, conflicts with neighbors or friends, financial problems.[9] The second part

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sought information on enuresis (type, time, and frequency or severity of enuresis), family history of enuresis, and medical history of the child including sleep disorders including disorders in initiating and maintaining sleep (like snoring, difficult arousal, sleep breathing disorders, and insomnia). Parents were told that any information received would be kept private and anonymous. Two pediatric experts and two community medicine consultants in the field of research methodology validated the questionnaire.

The type of SCD was recorded for all patients depending on baseline hemoglobin electrophoresis and / High Performance Liquid Chromatography (HPLC) results. Blood samples were collected for complete blood count using Automated Hematology Analyzer. The urine samples sent for analysis were the first-voided morning, clean-catch mid-stream samples. Specific gravity was measured using dipstick urinalysis (ACON Laboratories, Inc., USA). A urinalysis was done to check for urinary tract infection, and those with positive results were sent for urine culture and sensitivity. Urine albumin was determined using immunoturbidimetric assay. Urinary creatinine was measured by the alkaline picrate method. The urinary albumin/creatinine ratio (ACR) was computed and classified as normal when it was less than 30mg/g, microalbuminuria (ACR= 30-300 mg/g), or macroalbuminuria (ACR more than 300 mg/g). [-10]

The way of urine collection was explained to the parents/ caregivers and older participants.

Enuresis was applied when the child has a "repeated involuntary or unintentional urine voiding into the bed or clothes that occurs exclusively during sleeping periods and not related to medication by the age of five years or older, with a minimum frequency of once monthly for at least three consecutive months" [3,11,12] Secondary enuresis is reserved for children who have been dry for more than 6 months. Otherwise, it is referred to as primary enuresis. [12] Hyposthenuria was defined as urine specific gravity <1.010 on dipstick analysis. [13]

Statistical analysis

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Data were compiled and analyzed by the SPSS version 23.0 software (IBM Corp, Armonk, New York, USA). The t-test, Chi square test, or Fisher's Exact test were used for comparison of covariates where applicable. Binary logistic regression analysis was done to look for the possible independent risk factors associated with enuresis. The level of significance was chosen at a P-value of <0.05.

Ethical consideration

The Ethical Committee of the College of Medicine, University of Basrah authorized this study. Before the children were included in the research, their parents provided informed consent.

Results

Out of 200 eligible children, 161 were studied after exclusion of 39 based on the exclusion criteria, yielding an 80.5% response rate, with 98 (60.9%) males and 63 (39.1%) females; their mean age was 10.9±2.9 years (10.9±2.8 for males and 11.0±3.1 for females). Of the participants, children 50 (31.1%) were found to have enuresis. Of enuretic children, 45 (90%) had primary enuresis and 5 (10%) had secondary enuresis. Diurnal enuresis was reported in 4 (8%), nocturnal in 33 (66%), and both diurnal and nocturnal in 13 (26%). Daily enuresis was found in 22 (44%) children, several times/week in 15 (30%), once/week in 5 (10%), and once or more per month in 8 (16%). [Table 1]

No significant difference was noticed between children with and without enuresis regarding age, sex, birth order, family income, stressful life events, and parents' level of education. However, family history of enuresis, and higher number of siblings were found to be significantly associated with enuresis [Table 2].

All children included in the study have sickle cell anemia and sickle/ β- thalassemia. None was found to have other types of SCD. In univariate analysis, children with enuresis exhibited a significantly higher proportion of hyposthenuria than those without enuresis (24.0% vs. 6.3%, P=0.002). Although enuretic children had a higher percentage of sleep disorders and hospitalization rate and frequency during the previous 12 months than non-enuretic, the difference was not found to be significantly different. Furthermore, hemoglobin genotype, albuminuria, and serum hemoglobin

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level, and red blood indices values (MCH, MCV, and MCHC values) were not significantly different between the two groups [Table 3].

Among SCD studied patients, three variables were found to be independent predictors of enuresis. These were family history of enuresis (odd ratio (OR), 5.94; 95% CI, 2.54-13.89; *P*<0.001), hyposthenuria (OR, 3.76; 95% CI, 1.25-13.30; *P*=0.018) and sleep disorders (OR, 2.90; 95%CI, 1.19-7.06; *P*= 0.019) [Table 4]. In contrast, none of the other investigated variables was shown to be independent predictors of enuresis.

Discussion

Our study has revealed that prevalence rate of enuresis was 31.1% among sickle cell disease pediatric patients. Other studies have reported varying rates of enuresis in this group of patients; in the United Kingdom, London (35.7%), [14] Sudan (38%), [15], Saudi Arabia (48.6%), [16] and Nigeria (49.4%). [11] Such variation in the prevalence rates might be due to disparities in the definition of enuresis, sampling method, [17] socio-cultural differences, and study design whether population or health institute based studies. [18] Earlier studies in Iraq showed lower prevalence of enuresis among children without SCD, which ranges from 7.5% - 29.5%. [18-20] Many studies have consistently found a strong relationship between sickle cell disease and enuresis. [21,22] Sickle cell disease significantly affects renal structure and function, reflected in a variety of renal syndromes and diseases including abnormal hemodynamics, glomerulopathies, and hyposthenuria (impaired urinary concentrating ability). [23]

The logistic regression analysis showed that hyposthenuria was independently and significantly associated with enuresis (OR, 3.76; 95% CI, 1.25-11.30; *P*= 0.018). A long before, [24] hyposthenuria-induced nocturnal polyuria was thought to be the cause of nocturnal enuresis in sickle cell anemia (SCA) patients. This theory is reinforced by the fact that hyposthenuria is a common and early infarction-related renal complication. [25] Ugwu et al. later demonstrated the same results. [26] However, Eneh et al. [7] and Readett et al. [27] found no association between enuresis and hyposthenuria, and after water deprivation, SCD children with enuresis had the same maximum voided urine volume as those without enuresis. They attributed enuresis to reduced

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functional bladder capacity and other factors such as social and environmental influences and decreased arousal during sleep. [7,27]

Factors other than hyposthenuria were found to be significantly and independently associated with enuresis. Family history of enuresis was found to be an independent predictor of enuresis with an adjusted odds ratio of 5.94 (95% CI, 2.54-13.89; $P<0.001$). A result, that has been reported before. [18,28] Such association highlights the importance of genetic roots in the etiology of enuresis. [28]

Although the rate of sleep disorders was higher in enuretic children (30.0%) compared to 17.1% in non-enuretic children in univariate analysis, the difference was not significant (P=0.064). However, after adjustment for other variables, sleep disorders were observed to be an independent predictor for enuresis (adjusted OR, 2.90; 95% CI, 1.19-7.06; $P=0.019$). Other studies have found that children with SCD are more likely to have sleep difficulties, which cause them to be unable to awaken from sleep in response to a full bladder, resulting in enuresis. [29,30] A variety of factors, including pain, environmental, psychological, and treatment factors (which were not investigated in this study), have been reported to influence sleep disorders. [31] These factors might confound such relationship. The precise relationship between sleep disorders and enuresis needs to be further investigated. Furthermore, the absence of polysomnography and parents' reported data made defining sleep problems difficult. Lehmann et al who reported an association between sleep disorders and enuresis recommended that children with SCD and enuresis have to be referred to the pulmonologist for the evaluation of sleep- disordered breathing. [32]

Nocturnal enuresis in individuals with airway obstruction is thought to be caused by increased synthesis of atrial natriuretic peptide, which raises the arousal threshold during sleep. [33]

The aggregation of two or all of the three independent risk factors mentioned above was significantly higher in enuretic children than in non-enuretic children. In the enuretic children, 37 (74.0%) had 0-1 risk factor of the three independent risk factors, 11 (22.0%) had 2 risk factors, and 2 (4.0%) had all three factors, compared to 109

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(98.2%) who had 0-1 risk factor, 2 (1.8%) had 2 risk factors, and none (0.0%) had all three factors (P <0.001).

Family income, parents' level of education, and birth order did not affect the association with enuresis, a result that agrees with many previous studies.[20,34] However, other studies reported a significant impact of socio-economic status on enuresis prevalence rates. [15,35] Thus, it seems that there is no agreement on the significance of socio-economic status as a risk factor for enuresis. This could be attributed to the relative inaccuracy of social basic facilities in determining social rank or it might reflect the increased knowledge and awareness regarding health and health-related issues among all socioeconomic groups. [27]

Our findings revealed that the well-documented decrease in enuresis prevalence with age in children without SCD [20,36] was less evident in children with SCD, implying that some SCD-related morbidities, such as intravascular sickling and vaso-occlusion, improved less spontaneously in children with SCD. [25,37] This result is consistent with what other researchers have found. [11,37] Although enuresis is frequently reported to be more prevalent in boys than girls in children without SCD, [34] gender was not associated with enuresis in our study. This finding is consistent with the findings of Esezobor et al. [11] According to one possible theory, several sickle cell-related characteristics may be related to enuresis. Readett et al. [27] observed a higher rate of enuresis in children with hemoglobin SS, as well as a lower fetal hemoglobin level. In agreement with Esezobor et al., [11] no association was identified between enuresis and history of hospitalization during the 12 months preceding the study.

Though the number of siblings had a significant association with enuresis in univariate analysis (P= 0.018), the logistic regression analysis revealed no effect after adjusting for other variables. This result is consistent with that reported by others. [38] Our study is limited in that it was a cross-sectional study; thus, no causal relationships between variables could be established. Furthermore, polysomnography was not done to assess the pattern of sleep disordered breathing. Recall bias cannot be entirely eliminated. The form and content of questions, as well as connecting exposure to specific life events, may all have an impact on recall accuracy. SCD impacts the

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psychosocial and quality of life in general, therefore, parents who have children with the disease are more likely to recall previous exposure of their children.

The study's strength is that it is the first in Iraq to measure the prevalence and determinants of enuresis in children with SCD, with special emphasis on the most controversial determinant, hyopsthenuria.

Conclusions

Enuresis is common in pediatric patients with sickle cell disease. Hyposthenuria, family history of enuresis, and sleep disorders were significant independent predictors of enuresis. Children with sickle cell disease, especially those with a family history of enuresis, should be assessed frequently for enuresis and kidney function.

Authors' Contributions

JN, MK and AM designed and planned the study. AM and DS collected the data. JN and MK contributed to the data analysis and drafting of the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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Table 1: Types of enuresis reported among studied SCD patients

Variable	No.	%
Onset of enuresis		
Primary	45	90
Secondary	5	10
Time of enuresis		
Diurnal	4	8
Nocturnal	33	66
Both	13	26
Frequency		
Daily	22	44
Several times/ week	15	30
Once/week	5	10
Once or more/month	8	16
Total	**50**	**100**

Table 2: Association of enuresis with socio-demographic characteristics

Variable	Enuresis	No enuresis	*P*- value
Age (years), Mean ±SD	10.4±2.8	11.2±2.9	0.119
Age (years)			0.369
6-7	9 (18.0)	21 (18.9)	
8-9	11 (22.0)	13 (11.7)	
10-11	10 (20.0)	20 (18.0)	
12-13	11 (22.0)	24 (21.6)	
14-15	9 (18.0)	33 (29.7)	
Male sex, No. (%)	34 (68.0)	64 (57.7)	0.228
No. of siblings, No. (%)			0.018
0	4 (8.0)	1 (0.9)	
1	2 (4.0)	11 (9.9)	
2	5 (10.0)	21 (18.9)	
3	9 (18.0)	33 (29.7)	
4	12 (24.0)	18 (16.2)	
5 & more	18 (36.0)	27 (24.3)	
Birth order, No. (%)			0.316
First	12 (24.0)	37 (33.3)	
Second	11 (22.0)	33 (29.7)	
Third	12 (24.0)	22 (19.8)	
Fourth	5 (10.0)	7 (6.3)	

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Fifth or higher	10 (20.0)	12 (10.8)	
Family history of enuresis, No. (%)			<0.001
Yes	24 (48.0)	16 (14.4)	
No	26 (52.0)	95 (85.6)	
Per capita family monthly income (IQD), No. (%)			0.402
<2500,000	33 (66.0)	84 (75.2)	
250,000 -500,000	15 (30.0)	22 (19.8)	
> 500,000	2 (4.0)	5 (4.5)	
Father's education (years)			0.418
< 12	41 (82.0)	83 (74.8)	
≥ 12	9 (18.0)	28 (25.2)	
Mother's education (years)			0.412
< 12	37 (74.0)	89 (80.2)	
≥ 12	13 (26.0)	22 (19.8)	
Stressful life's event			0.101
Yes	15 (30.0)	20 (18.0)	
No	35 (70.0)	91 (82.0)	
Total	**50 (31.1)**	**111 (68.9)**	

No.= number, IQD= Iraqi Dinar

Table 3: Association of enuresis with certain clinical characteristics

Variable	**Enuresis n= 50**	**No enuresis n= 111**	***P*-value**
Hemoglobin genotype, No. (%)			0.999
SCA	23 (46.0)	52 (46.8)	
SC/ thalassemia	27 (54.0)	59 (53.2)	
Hyopsthenuria, No. (%)	12 (24.0)	7 (6.3)	0.002
Sleep disorders, No. (%)	15 (30.0)	19 (17.1)	0.064
Hospitalization during the last year, No. (%)	42 (84.0)	78 (72.2)	0.115
Frequency of hospitalization, No. (%)			0.068
No	8 (16.0)	33 (29.7)	
1-3 times	13 (26.0)	33 (29.7)	
4-6 times	14 (28.0)	29 (26.1)	
>6 times	15 (30.0)	16 (14.5)	
Albuminuria (mg/g), No. (%)			0.296
< 30	43 (86.0)	89 (80.2)	
30 -300	2 (4.0)	13 (11.7)	
>300	5 (10.0)	9 (8.1)	
Hb (g/dl)	9.4 ± 1.7	9.4 ± 0.9	0.954
MCH (pg/cell), Mean± SD	25.5±5.0	26.9±3.6	0.579
MCV (fl), Mean± SD	75.5±11.4	80.8±9.7	0.408
MCHC (gm/dl), Mean± SD	33.5±1.7	33.2±1.2	0.742

No.= number, SCA= sickle cell anemia, SC= sickle cell, Hb= hemoglobin, MCH= mean corpuscular hemoglobin, MCV= mean corpuscular volume, MCHC= mean corpuscular hemoglobin concentration

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418

419 **Table 4:** Logistic regression analysis

Parameter	**β Coefficient**	**OR**	**95% CI for OR**		***P*-value**
			Lower	**Upper**	
Family history of enuresis	1.781	5.94	2.54	13.89	<0.001
Hyposthenuria	1.326	3.76	1.25	11.30	0.018
Sleep disorders	1.066	2.90	1.19	7.06	0.019

420

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